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Cu-Catalyzed *N*- and *O*-Arylation of 2-, 3-, and 4-Hydroxypyridines and Hydroxyquinolines

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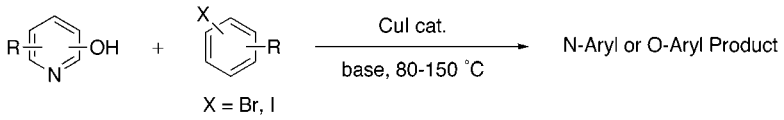
ABSTRACT



With use of Cu-based catalysts, 2- and 4-hydroxypyridines were *N*-arylated in modest to excellent yields. In the case of 2-hydroxypyridine, the use of 4,7-dimethoxy-1,10-phenanthroline, 3, expanded the scope of previous literature reports to include the use of *N*-containing heteroaryl halides, and 2-substituted aryl halides. In addition, by using a copper catalyst based on 2,2,6,6-tetramethylheptane-3,5-dione, 4, the first *N*-arylations of 4-hydroxypyridines and *O*-arylations of 3-hydroxypyridines with aryl bromides and iodides have been accomplished.

N-Aryl 2- and 4-hydroxypyridines and *O*-aryl 3-hydroxypyridines manifest significant biological activities[1] and exhibit interesting photochemical properties.[2] The successful *N*- and *O*-arylation of 2-, 3-, and 4-hydroxypyridines with aryl halides has not been reported with the use of Pd-based methods;[3,4] however, the use of Cu for this transformation has been described.[5] Although the Cu-mediated cross-coupling of 2-hydroxypyridines with aryl boronic acids,[6] aryl stannanes,[7] and aryl bismuth reagents[8] has been previously reported, aryl halides are preferred substrates as these electrophiles tend to be more stable, easier to prepare, and/or less toxic than the corresponding B, Sn, and Bi counterparts. Several accounts of the Cu-catalyzed *N*-arylation of 2-hydroxypyridines with aryl halides have been reported without the use of added ligand and with ligands **1**, **2**, and **5**.[9] However, the Cu-catalyzed *N*- and *O*-arylations of 4- and 3-hydroxypyridines, respectively, are yet to be disclosed. Herein, we describe our recent progress in coupling hydroxypyridines and hydroxyquinolines with aryl halides.

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Previous accounts of the Cu-catalyzed *N*-arylation of 2-hydroxypyridine with *N*-containing aryl halides reported that many substrates were incompatible with the methods.[9] First, *N*-containing heteroaryl halides could not be utilized. Li proposed that the coordination of the sp^2-hybidized nitrogen lone pair electrons of these electrophiles to the copper catalyst impeded the cross-coupling reaction.[9d] Second, ortho-substituted aryl halides were unreactive, as a maximum yield of 2% was reported for the reactions of 2-hydroxypyridines with such substrates.[9] This finding agrees with the well-established notion that Cu-catalyzed C-heteroatom bond-forming reactions of aryl halides are particularly sensitive to steric hindrance on the electrophilic component.[6] Finally, 2-hydroxypyridines bearing strongly electron-withdrawing groups or containing substituents at the 6-position were also unreactive.[9d−f]

While ligands **1** and **2** were first designed and reported for reactions of Cu-catalyzed *N*-arylations of indoles[10] and amides[11] ($pk_a \sim 21-26$), using aryl iodides and bromides, 2-hyroxypyridine is significantly more acidic ($pk_a \sim 17$).[12] Since the pk_a of imidazole ($pk_a \sim 19$) is closer to that of the hydroxypyridine, we felt that a good catalyst system for the *N*-arylation of imidazoles[13] might also be effective for the *N*-arylation 2-hydroxypyridines.

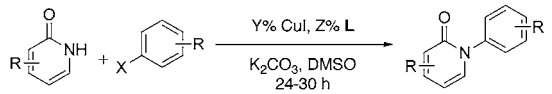
We recently reported that a catalytic system based on Cu_2O, 4,7-dimethoxy-1,10-phenanthroline (**3**) as a ligand, and poly(ethylene glycol) as an additive was efficient for promoting the *N*-arylation of imidazoles. Using a combination of CuI and **3**, we found that *N*-containing heterocyclic aryl halides could be coupled to 2-hydroxypyridine in modest to good yields (Table 1 entries 1−4). The reactions of 2-hydroxypyridine with aryl iodides and bromides can be successfully accomplished even in the presence of free N−H groups (Table 1, entries 3 and 6). By using this catalyst system, a nonconjugated electron-withdrawing group at the 5-position was tolerated (Table 1, entry 7). However, 2-hydroxy-3-methyl-5-nitropyridine was unreactive, presumably due to the decreased coordinating ability (nucleophilicity) of the hydroxypyridine (Table 1, entry 8).

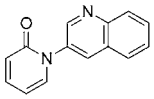
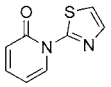
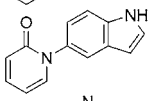
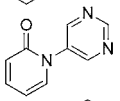
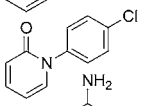
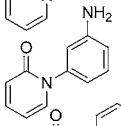
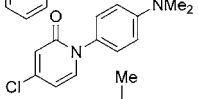
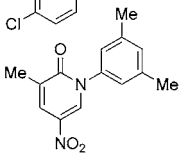
In our own attempts to improve the reaction of 2-hydroxypyridine with hindered aryl iodides, we discovered that a mixture of *N*- and *O*-aryl products was produced under the reaction conditions, with the latter being the major product. This phenomenon had not been previously reported for reactions of this type.[9] Using **5** as a ligand, we were able to achieve modest selectivity for coupling the 2-substituted aryl halides with 2-hydroxypyridine to afford moderate yields of 2-pyridylaryl ethers (Table 2). Under more forcing conditions, the selectivity changed from O to N, providing the *N*-aryl product in poor yield with **3** as a ligand. Interestingly, although *N*-arylation is the preferential pathway for the Cu-catalyzed arylation of 2-hydroxypyridines with unhindered aryl halides, the milder conditions for achieving the *O*-aryl product when using hindered aryl iodides suggest that the inherent preference for C−N bond-formation over C−O can be overcome by steric effects. While the procedures are not very selective, they do provide access to usable amounts of both the *N*-aryl and *O*-aryl products.

Although we have shown that **3** is a better ligand than diamines **1** and **2** for Cu-catalyzed reactions of 2-hydroxypyridine with *N*-containing heteroaryl halides and with 2-substituted aryl iodides, commercially available ligands **1**−**2** and **5** are still viable alternatives for other coupling transformations of 2-hydroxypyridines with aryl halides.

Attempts to arylate 2-hydroxy-6-methylpyridine were met with limited success, even under forcing conditions. Presumably, the hindered amide coordinates too poorly to Cu(I) for the catalytic reaction to proceed. If the substrate does

Table 1. *N*-Arylation of 2-Hydroxypyridines[a]



entry	product	X	L	Y/Z	temperature (°C)	yield[b] (%)
1		Br	**3**	5/7.5	110	82[c]
2		Br	**3**	5/7.5	110	85[c]
3		I	**1**	10/20	100	75
4		I	**3**	5/7.5	110	47
5		I	**3**	10/15	110	80
6		Br	**3**	5/7.5	110	78
7		Br	**3**	10/15	120	71
8		I	**3**	10/15	80-150	0

[a] General reaction conditions: 1.2 mmol of 2-hydroxypyridine, 1.0 mmol of ArX, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO under Ar or N_2 atmosphere. [b] Isolated yield. [c] DMF used as solvent.

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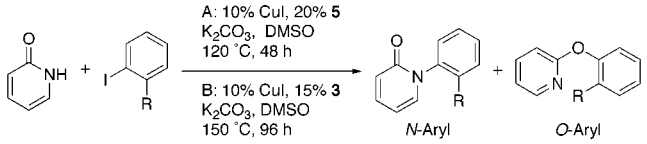
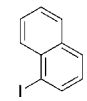
Table 2. Arylation of 2-Hydroxypyridine with Hindered Aryl Iodides



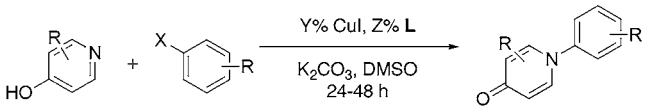
entry	ArI	conditions[a]	*N*-Aryl : *O*-Aryl[b]	yield of major product[c] (%)
1		A	1.0 : 4.8	67
2		B	1.8 : 1.0	40
3		A	1.0 : 4.0	64
4		B	1.6 : 1.0	42

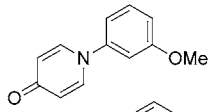
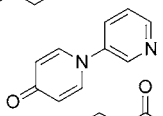
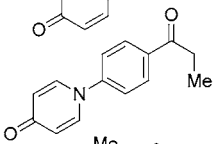
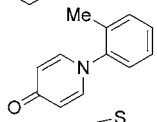
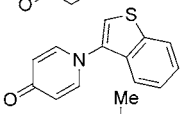
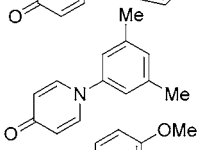
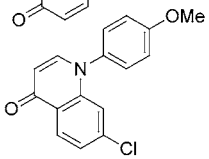
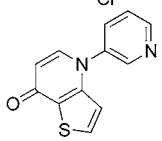
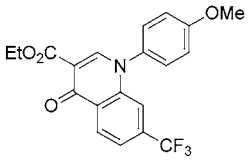
[a] Conditions A: 1.2 mmol of 2-hydroxypyridine, 1.0 mmol of ArI, 0.10 mmol of CuI, 0.15 mmol of **3**, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO at 150 °C for 96 h under Ar or N_2 atmosphere. Conditions B: 1.2 mmol of 2-hydroxypyridine, 1.0 mmol of ArI, 0.10 mmol of CuI, 0.20 mmol of **5**, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO at 120 °C for 48 h under Ar or N_2 atmosphere. [b] Detected by GC Analysis. [c] Isolated yield.

coordinate at N1, the methyl presumably impedes the aryl halide from interacting with the metal. On the other hand, if the methyl group provides too much hindrance to coordinate at nitrogen, the resulting **L**-Cu(I)-O species might not react with the aryl halide, to form the *O*-aryl product.

Since with Cu-catalysis 2-hydroxypyridines reacted preferentially with aryl halides at nitrogen instead of at oxygen, we became interested in exploring the selectivity difference between the *N*- and the *O*-positions for 4-hydroxypyridines. Previous investigations have shown that, depending on the nature of the electrophile, reactions of 4-hydroxypyridine with an electrophile can form the *O*-substituted product as the major product, the *N*-substituted product as the major product, or mixtures of the *N*- and *O*-substituted products.[14] No *O*-arylation was detected in reports of the uncatalyzed *N*-arylation of 4-hydroxypyridine with activated aryl chlorides,[17] or in the Cu(II)-mediated vinylation with tetravinyl tin[15] or arylation with arylboronic acids.[16] Similarly, we have found that the Cu(I)-catalyzed coupling of 4-hydroxypyridine with a variety of aryl and heteroaryl iodides and bromides showed complete selectivity for reaction at nitrogen using ligands **3** and **4** (Table 3).[17] The use of other *N*- and *O*-based chelating ligands, including **1**, **2**, and **5,** provided significantly lower yields of the *N*-substituted product. Only when using 2-iodotoluene as the electrophile did we detect trace amounts of *O*-aryl product as identified by GC/MS (Table 3, entry 4). However, we were unable to achieve selectivity for formation of the aryl 4-pyridyl ether as the major product

Table 3. *N*-Arylation of 4-Hydroxypyridines and Conjugated Hydroxyquinolines[a]



entry	product	X	L	Y/Z	temperature (°C)	yield[b] (%)
1		Br	**3**	5/7.5	110	95
2		Br	**3**	7/7.5	110	89
3		Br	**4**	5/20	110	92
4		I	**4**	10/40	110	63
5		Br	**4**	10/40	110	76
6		I	**4**	2/8	110	90
7		I	**4**	10/40	120	68[c]
8		I	**4**	10/40	120	65[c]
9		I	**4**	10/40	140	0

[a] General reaction conditions: 1.2 mmol of hydroxypyridine, 1.0 mmol of ArX, 2.0 mmol of K_2CO_3, 1.0 mL of DMSO under Ar or N_2 atmosphere. [b] Isolated yield. [c] K_3PO_4 used as base.

using a variety of conditions and ligands. Reactions of 4-hydroxyquinolines were accomplished by employing a stronger base and slightly higher temperatures (Table 3, entries 7 and 8). As with 2-hydroxypyridines, a 4-hydroxyquinoline with an electron-withdrawing group conjugated with the nitrogen was unreactive toward an aryl iodide under a variety of conditions (Table 3, entry 9).

For the 2- and 4-hydroxypyridines, we tentatively propose that the selectivity favoring *N*-arylation occurs due to one of two factors. If the Cu−N binding affinity is significantly stronger than that for the Cu−O bond, isomerization from Cu−N to Cu−O might be slower than aryl halide activation.

(14) For a brief summary, see: You, F.; Twieg, R. J. *Tetrahedron Lett.* **1999**, *40*, 8759.

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(16) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757.

(17) An authentic sample of 4-(3-methoxyphenoxy)pyridine was independently synthesized by uncatalyzed nucleophilic substitution of 4-chloropyridine with 3-methoxyphenol and compared to 1-(3-methoxyphenyl)-1*H*-pyridin-4-one (Table 5, entry 1) to verify that the product of Cu-catalysis was not the *O*-aryl compound.

Thus the *N*-aryl product would form selectively. In the case that a non-negligible amount of the Cu−O species is present in solution, the selectivity might be due to a lower activation barrier for oxidative addition to the Cu−N species. Further work is necessary to interrogate these hypotheses.

For 3-hydroxypyridine and related compounds, *N*-arylation is not a viable reaction pathway, and exclusive *O*-arylation might be possible. In our previous attempts to *O*-arylate 3-hydroxypyridines with aryl halides (using Pd catalysts), none of the desired product was observed.[4] To construct the aryl-3-pyridyl ether structure, it was necessary to cross-couple the 3-halopyridine with a phenol.

We have found that using a system based on CuI and 2,2,6,6-tetramethylheptane-3,5-dione, **4**,[18] 3-hydroxypyridines were successfully coupled with aryl bromides. The use of other *N*- and *O*-based chelating ligands in this reaction, including those depicted in Figure 1 and other β-diketones,[19]

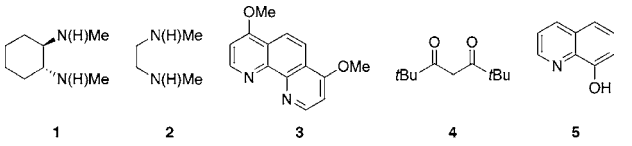
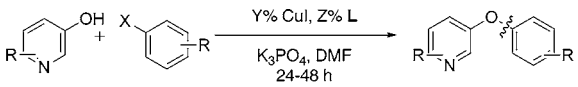
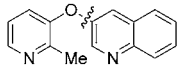
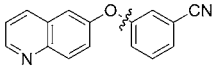
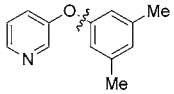
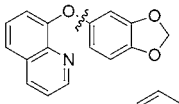
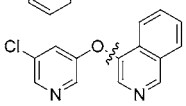
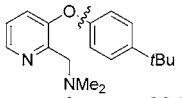
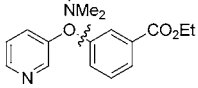


Figure 1. Ligands employed for *N*- and *O*-arylation of hydroxypyridines.

provided lower conversions and yields of product. Reactions of 3-hydroxypyridines with aryl halides containing water and/or base-sensitive functional groups could be accomplished at a lower temperature (80 °C) with the addition of molecular sieves to prevent hydrolysis of the nitrile and ester groups (Table 4, entries 2 and 7). The reaction of an aryl bromide was successful with a catalyst loading of 1% Cu, making this one of the most efficient Cu-catalyzed *N*- or *O*-arylation reaction of an aryl bromide reported to date (Table 4, entry 3). To *O*-arylate 8-hydroxyquinoline (Table 4, entry 4), ligand was not necessary, although more forcing conditions were required to achieve complete conversion of the aryl halide. In contrast, the presence of a neighboring coordinating group on the nucleophile has been demonstrated to accelerate the *N*-arylation of α-amino acids significantly.[20] The requirement for more strenuous conditions to *O*-arylate 8-hydroxyquinoline is not surprising since it is an effective ligand for Cu-catalyzed *O*-arylation reactions of phenols.[21] Reactions of 3-hydroxypyridines with 3-bromoquinoline and 4-bromoisoquinoline were successful (Table 4, entries 2 and 6). This is notable, since the 3-pyridyl-3′-(iso)quinolinyl ether structure cannot be accessed by other direct routes such as Pd-catalyzed methods or S_NAr of the corresponding 3-halopyridine under mild conditions without further activation (e.g., using 3-hydroxypyridine *N*-oxide). Under standard reaction conditions, the use of an aryl iodide gave significant amounts of diaryl ether as a byproduct. However, by using 4 Å molecular sieves and Cs_2CO_3 as a base,[22] a higher yield of aryl-pyridyl ether could be obtained (Table 4, entry 8).

Table 4. *O*-Arylation of 3-Hydroxypyridine and Nonconjugated Hydroxyquinolines[a]



entry	product	X	L	Y/Z	temperature (°C)	yield[b] (%)
1		Br	4	5/20	110	82
2		Br	4	10/40	80	78[c]
3		Br	4	1/4	120	91
4		Br	4	10/40	130	56[d]
5		Br	4	10/40	120	69
6		Br	-	10/0	110	77
7		I	4	10/40	80	91[e]

[a] General reaction conditions: 1.2 mmol of hydroxypyridine, 1.0 mmol of ArX, 2.0 mmol of K_3PO_4, 1.0 mL of DMF under Ar or N_2 atmosphere. [b] Isolated yield. [c] MeCN used as solvent with 3 Å molecular sieves. [d] DMSO used as solvent. [e] Cs_2CO_3 used as base with 3 Å molecular sieves.

In conclusion, we have developed a series of catalysts for the *N*- and *O*-arylation of hydroxypyridines and hydroxyquinolines. Future efforts will be devoted both to maximizing the efficiency and scope of this method as well as to determining the mechanistic basis behind the observed selectivity.

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Supporting Information Available: Experimental procedures and characterization data for all new and known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062904G

(18) This ligand was originally reported by Merck chemists for the Cu-catalyzed *O*-arylation of phenol. See: Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623.

(19) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(20) For an example, see: Ma, D.; Yongda, Z.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(21) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043.

(22) Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. S.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913.